UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	[illegible]
08/078,768	06/16/93	TULLIS

R PM89658

MARTINELL, J

18M2/0504

TOWNSEND & TOWNSEND, KHOURIE & CREW
ONE MARKET
STEUART STREET TOWER
20TH FLOOR
SAN FRANCISCO, CA 94105

1804 35

05/04/95

Below is a communication from the EXAMINER in charge of this application

COMMISSIONER OF PATENTS AND TRADEMARKS

ADVISORY ACTION

☒ THE PERIOD FOR RESPONSE:

a) ☒ is extended to run 5 months or continues to run _____ from the date of the final rejection

b) ☐ expires three months from the date of the final rejection or as of the mailing date of this Advisory Action, whichever is later. In no event however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition , and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

☐ Appellant's Brief is due in accordance with 37 CFR 1.192(a).

☒ Applicant's response to the final rejection, filed 04/17/95 has been considered with the following effect, but it is not deemed to place the application in condition for allowance:

1. ☐ The proposed amendments to the claim and /or specification will not be entered and the final rejection stands because:

   a. ☐ There is no convincing showing under 37 CFR 1.116(b) why the proposed amendment is necessary and was not earlier presented.

   b. ☐ They raise new issues that would require further consideration and/or search. (See Note).

   c. ☐ They raise the issue of new matter. (See Note).

   d. ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

   e. ☐ They present additional claims without cancelling a corresponding number of finally rejected claims.

   NOTE: _____

2. ☐ Newly proposed or amended claims _____ would be allowed if submitted in a separately filed amendment cancelling the non-allowable claims.

3. ☒ Upon the filing an appeal, ~~the proposed amendment ☐ will be entered ☐ will not be entered and~~ the status of the claims will be as follows:

   Claims allowed: None.
   Claims objected to: None.
   Claims rejected: 64-72.

   However;

   ☐ Applicant's response has overcome the following rejection(s): _____

4. ☒ The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection, ~~because~~ See following pages.

5. ☐ The affidavit or exhibit will not be considered because applicant has not shown good and sufficent reasons why it was not earlier presented.

☐ The proposed drawing correction ☐ has ☐ has not been approved by the examiner.

☐ Other

Applicant's arguments (paper no. 33) and the declarations by Drs. Schwartz and Ruth (filed April 17, 1995) and the attachments are not convincing. Accordingly, the rejection under 35 U.S.C. § 112, first paragraph stands for reasons already of record. The following is added in rebuttal to arguments advanced by applicant and is not an invitation to submit further argument, amendment, or evidence subsequent to the final rejection.

(a) Applicant's arguments under section A of paper no. 33 are not convincing. Applicant asserts that, "The Examiner has previously urged that at the time of filing of the parent application in October of 1981, there were no other stabilized oligonucleotides reported in the literature." This assertion is made without reference to where in the file such an "urging" appears. Reference to the Office action mailed December 16, 1992 reveals the actual issue, which is that the instant application fails to guide those of skill in the art as to which oligodeoxyribonucleotides to use. Hence, all of applicant's arguments in connection with the existence of any particular form of oligodeoxyribonuceotide at any time prior to the filing of th instant application are most unconvincing in the absence of a mention or teaching in the application as to how to use them. In fact, the instant application fails to even mention the different forms of oligodeoxyribonucleotides in any specific manner.

(b) Applicant's arguments and remarks in section B of paper no. 33 are most unconvincing because applicant has misidentified the statutory basis of the rej ction. Applicant acknowledg s (page 8)

that the examiner has previously explained to applicant that the statutory basis of the rejection is 35 U.S.C. § 112, first paragraph and does not include 35 U.S.C. § 101 (utility). Accordingly, applicant's arguments in connection with utility are superfluous at best, but are given no weight at all whatsoever in connection with the rejection under 35 U.S.C. § 112, first paragraph. Applicant additionally argues (page 11) that several references support the notion that intact oligonucleotides can be delivered to animals and isolated cells. This argument is not convincing because each of the articles cited was published subsequent to the effective filing date of the instant application. In addition, the following are noted.

(1) Michelson et al (Exhibit 3) does not disclose the use of a single stranded oligonucleotide, but is concerned only with the stability of a double stranded RNA in vivo. Applicant fails to argue and the declarations fail to reveal how an already double stranded molecul could have any function at all as an antisense molecule, nor do the argument or declarations say what relevance the stability of a double stranded molecule has to the stability of a single stranded molecule. Indeed, applicant simply submits the article, discloses the fact that the articl was submitted, and makes no connection between the instant application, claims, or rejection and the article.

(2) Wolff et al (Exhibit 4) is not convincing. First, applicant incorrectly attributes disclosures in Wolff et al to Michelson et al (paper no. 33, page 11 and pages 6 of each of the declarations by Drs. Ruth and Schwartz). Second, the reference says nothing at all about single stranded oligonucleotides.

(3) Lin et al (Exhibit 5) and the arguments in connection with it are not convincing because the reference does not deal with single stranded oligonucleotides.

(4) Wolff et al (Exhibit 6) and the arguments in connection with it are not convincing because the reference does not deal with single stranded oligonucleotides.

(5) Each of Phillips et al (Exhibit 7), Akabayashi et al (Exhibit 8), and Hijya et al (Exhibit 9) teaches the use of oligodeoxyribonucleotides in vivo. Applicant's reliance on these references to complete the application is insufficient because each of these references was published in 1994, which is after the effective filing date of the instant application.

(c) Applicant argues (paper no. 33, section C) that the examiner misinterpreted a statement made by the inventor during the prosecution history of a prior application. Applicant's argument is unconvincing in the face of the simple, direct, and unambiguous language used by the inventor. Applicant's arguments are further

unconvincing in view of published statements under the name of the inventor and others. For example, in the publication by Tullis et al (Biotechnology International, 1992, reference A15, already of record) state on page 79 that one of the key events in the development of antisense technology was the development was more efficient systems for the synthesis of normal and phosphorous modified oligodeoxyribonucleotides and then goes on to cite a number of references, all of which were published subsequent to the effective filing date of the instant application. (The Beaucage and Caruthers reference is listed as being published in 1980 at page 79, but is listed as published in 1984 in the bibliography. The 1984 date is almost certainly correct because the Beaucage and Caruthers reference is a European Patent application that was filed in 1982.) Additionally, at page 80 (top part of the right hand column), Tullis et al mention problems with uptake and stability of unmodified oligonucleotides and give no clue to the reader to do any of the things that applicant now asserts would have been obvious to anyone of skill in the art in 1981. Thus, the evidence in the record indicates that applicant himself did not know that unmodified oligonucleotides could be used as antisense agents even as late as 1992.

(d) Applicant's argument in paper no. 33, section D is unconvincing. Applicant again incorrectly refers to a hybrid rejection under 35 U.S.C. §§ 101 and 112. Applicant then asserts that, "Once the inventive aspects of the oligonucleotides are recited, the

practice of the invention is trivial . . . ." The argument fails to persuade because the premise is grounded in an incorrect assumption. The very issue here is whether the inventive aspect has been recited. In all the argumentation advanced by applicant, applicant fails to indicate where the application teaches or mentions the use of any specific modified oligonucleotides other than phosphotriesters or the use of unmodified oligonucleotides as antisense agents.

(e) Applicant's arguments (paper no. 33, section E) are unconvincing for reasons given in (a) - (d) above and reasons already of record.

Certain papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Art Unit 1804 at (703) 308-4312. The faxing of such papers must conform with the rules published in the Official Gazette, 1156 OG 61 (November 16, 1993).

Any inquiry concerning this communication should be directed to J. Martinell at telephone number (703) 308-0296.

JAMES MARTINELL, PH.D.
SENIOR LEVEL EXAMINER
GROUP 1800